

# Adult secondary hemophagocytic lymphohistiocytosis with cerebral and meningeal symptoms early after allogeneic hematopoietic stem cell transplantation

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A 28-year-old man with Ph-negative acute lymphoblastic leukemia was readmitted to the Bone Marrow Transplant Unit on day 42 after matched unrelated donor allogeneic hematopoietic stem cell transplantation (allo-HSCT), presenting with fever, general malaise, tonsillitis, lymphadenopathy, and splenomegaly. The pretransplant patient / donor cytomegalovirus (CMV) status was positive / negative, and the Epstein-Barr virus (EBV) status was positive / positive. On admission, a high blood EBV load ( $1.2 \times 10^5$  copies/ml) was detected. Due to progressing organomegaly and elevation of lactate dehydrogenase levels after standard treatment with rituximab ( $375 \text{ mg/m}^2$  intravenously [IV]),  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography-computed tomography was performed. It revealed abnormally increased metabolic activity in multiple enlarged lymph nodes and the spleen (FIGURE 1A and 1B). Because of pancytopenia progression, additional blood tests were performed. Prominent hyperferritinemia (ferritin levels,  $74\,000 \mu\text{g/l}$ ; reference range,  $13\text{--}400 \mu\text{g/l}$ ) with hypertriglyceridemia (triglyceride levels,  $3.73 \text{ mmol/l}$ ; reference range,  $<2.26 \text{ mmol/l}$ ) were noted. Peripheral blood lymphocyte immunophenotyping showed a sparse natural killer (NK) cell population. A tentative diagnosis of posttransplant lymphoproliferative disorder (PTLD), accompanied by hemophagocytic lymphohistiocytosis (HLH), was made.<sup>1,2</sup> Despite the administration of the second and third rituximab dose and a reduction of cyclosporine A (CsA) dosage,

the patient developed neurologic symptoms, particularly in the range of cortical activities: deterioration in verbal contact, memory impairment, and disorientation followed by coma. Brain magnetic resonance imaging suggested meningitis (FIGURE 1C and 1D). Cerebrospinal fluid analysis revealed high protein levels ( $283 \text{ mg/dl}$ ; reference range,  $20\text{--}40 \text{ mg/dl}$ ), pleocytosis (white blood cell count,  $70/\mu\text{l}$ ), and high EBV load ( $6.2 \times 10^3$  copies/ml). Subsequently, immunosuppression was modified: dexamethasone was introduced ( $8 \text{ mg}$  3 times daily) with complete CsA withdrawal. Due to the severity of the neurologic status, antiviral acyclovir was switched to foscarnet, and 3 doses of IV etoposide ( $100 \text{ mg}$ ) as well as 2 doses of intrathecal methotrexate ( $15 \text{ mg}$ ) were administered, in parallel with weekly rituximab (up to 5 infusions). The patient's general condition improved. Finally, the EBV clearance was achieved. A dose of systemic dexamethasone was gradually tapered, simultaneously with restarting CsA. At present, 5 years after the transplant, the patient is alive and remains in complete remission.

The EBV is a highly immunogenic  $\gamma$ -herpesvirus. Severely immunosuppressed patients develop B-cell proliferation and a diminished EBV-specific cytotoxic T-cell population.<sup>3</sup> B-cell PTLD associated with EBV is a life-threatening complication after allo-HSCT, resulting from an outgrowth of infected donor-origin B cells.<sup>3</sup> In patients after allo-HSCT, EBV is the second most common cause of viral encephalitis, after human

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Received: October 28, 2019.

Revision accepted: January 3, 2020.

Published online: January 14, 2020.

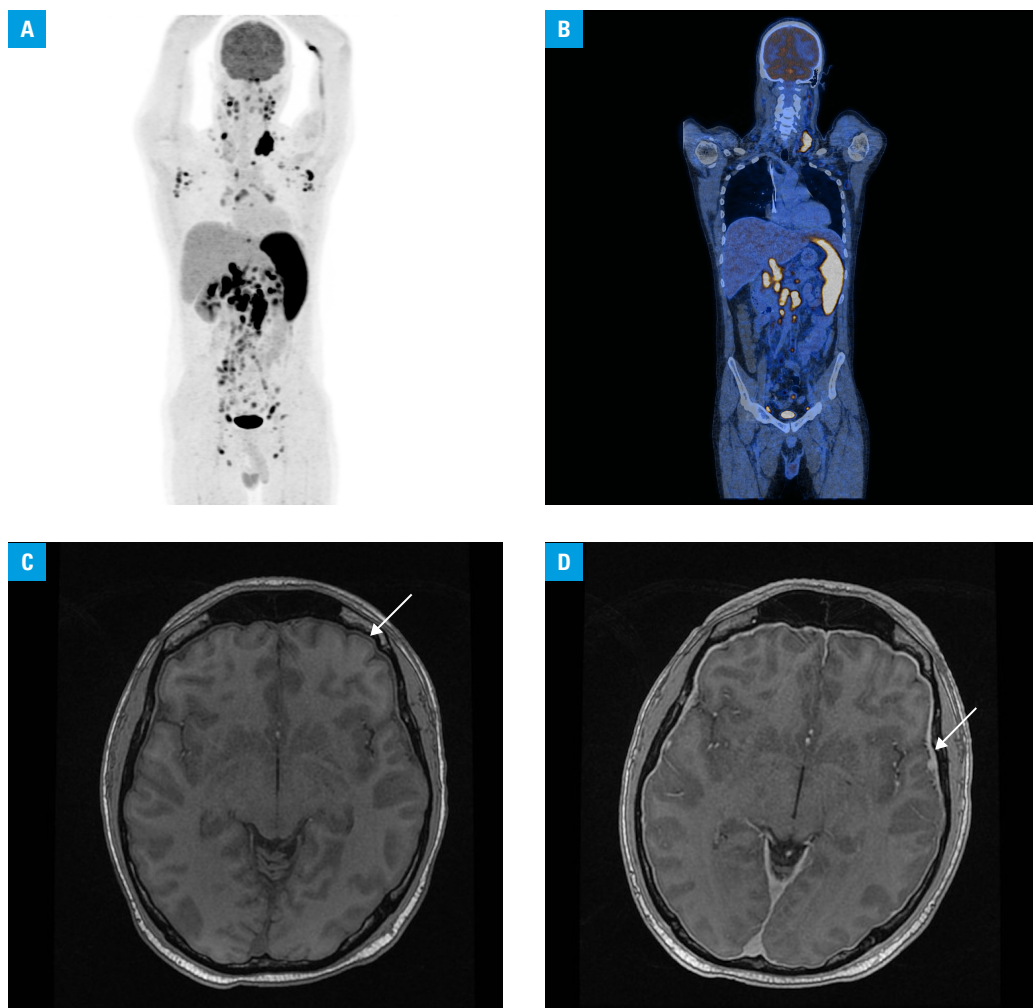
Pol Arch Intern Med. 2020;

130 (3): 246-248

doi:10.20452/pamw.15141

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**FIGURE 1** **A** –  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography–computed tomography ( $^{18}\text{F}$ -FDG PET/CT; coronal view): a maximal intensity projection scan showing an increased  $^{18}\text{F}$ -FDG uptake in the lymph nodes and spleen; **B** –  $^{18}\text{F}$ -FDG PET/CT (coronal view): a fusion scan showing a diffuse  $^{18}\text{F}$ -FDG uptake of the lymphoid tissue—the highest in the para-aortic, liver hilar, and pancreatic lymph node groups (maximum standardized uptake value [SUVmax], 18.8) and left-side neck lymph nodes (SUVmax, 16.6), while medium in the spleen (SUVmax, 10.7) and peripheral lymph nodes (SUVmax, 3.1–9.8); **C** – brain magnetic resonance imaging (MRI): a T1-weighted sequence showing global meningeal thickening (arrow); **D** – brain MRI: a T1-weighted sequence showing postcontrast meningeal enhancement (arrow)

herpesvirus 6.<sup>4</sup> Hemophagocytic lymphohistiocytosis, characterized by molecular abnormalities and clinical or laboratory findings such as fever, splenomegaly, cytopenia, reduced NK cell activity, hypofibrinogenemia, hemophagocytosis, and increased levels of soluble CD25 protein, ferritin, and triglycerides, has become more widely recognized in adults, predominately as a secondary disease.<sup>5</sup> The treatment strategy in EBV-driven HLH depends on the patient's condition, from short-term corticosteroids with or without immunoglobulins in less severe disease to intensive treatment with early etoposide administration in rapidly deteriorating patients.<sup>5</sup> There is no established standard of care in patients fulfilling the HLH-2004 diagnostic criteria for HLH after allo-HSCT. In our patient, based on the high EBV load and imaging, probable PTLD was diagnosed, complicated by HLH. The differential diagnosis should include EBV meningoencephalitis and advanced HLH with

central nervous system involvement. In our case, focusing on HLH as a major life-threatening event, the adoption of HLH-2004 therapeutic modalities provided an excellent clinical outcome in a rituximab-refractory disease. However, the negative pretransplant EBV immunity status in a donor and coreactivation of viruses may impede treatment.

## ARTICLE INFORMATION

**CONFLICT OF INTEREST** None declared.

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**HOW TO CITE** Mensah-Glanowska P, Trofimiuk-Möldner M, Grochowska A, et al. Adult secondary hemophagocytic lymphohistiocytosis with cerebral and meningeal symptoms early after allogeneic hematopoietic stem cell transplantation. *Pol Arch Intern Med.* 2020; 130: 246-248. doi:10.20452/pamw.15141

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